

REMARKS

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claims 41, 43, 45-46 and 50-52 have been amended for reasons of formality and grammar. No new matter is added by the amendments. Claim 44 has been cancelled without prejudice or disclaimer. Applicants reserve the right to preserve the subject matter of these claims in one or more continuation applications.

Petition for Extension of Time

It is noted that a two-month petition for extension of time is necessary to provide for the timeliness of the response. A request for such an extension is made extending the time for response from December 10, 2004 to February 10, 2005.

Withdrawn Objections/Rejections

Applicants acknowledge the withdrawal of the objection to the specification.

Applicants acknowledge the withdrawal of the objection to claim 48.

Applicants acknowledge the withdrawal of the rejection of claims 43-49 under 35 U.S.C. 103(a) as unpatentable over Ridgway, Carter (U.S. Pat. No. 5,807,706) or Carter (WO 96/27011) in view of Kostelney, and further in view of Vaughan.

Applicants acknowledge the withdrawal of the rejection of claims 30-42 under 35 U.S.C. 112, first paragraph.

Double Patenting

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 30-51 of copending Application No. 09/863,693. As stated in the previous Response, Applicants will file a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 47-63 of copending Application No. 09/520,130. As stated in the previous Response, Applicants will file a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-49 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-29 of copending Application No. 10/143,437. As stated in the previous Response, Applicants will file a terminal disclaimer, if appropriate, upon indication of allowable subject matter.

35 U.S.C. 112, first paragraph

Written Description

Claims 30-42 were rejected under 35 U.S.C. 112, first paragraph, for alleged new matter. The Examiner contends that the specification only teaches the use of the same light chain in all binding domains in the multispecific antibody. Applicants traverse this rejection.

The fundamental factual inquiry in whether the claims are sufficiently described "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *MPEP 2163 I.B.* Sufficient written description exists for a claim limitation if one of skill in the art can immediately discern the limitation from reading the original specification. *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 31 USPQ2d 1855 (Fed Cir. 1994). The specification need not, however, describe *ipsis verbis* what is recited in the claims; rather, the claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *MPEP 2163 I.B.* Furthermore, Applicants need not disclose in detail what is conventional or well known to one of ordinary skill in the art. *MPEP II 3(a)*. "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." *Id.*

Claims 30-42 recite methods of preparing multispecific antibodies comprising a first polypeptide and at least one additional polypeptide, wherein the light chains of the first and additional polypeptides each have three CDR regions, have at least 98% sequence identity, and only differ from one another at amino acid positions outside of the CDR regions. Applicants submit that one of skill in the art at the time of filing would have clearly understood from reading the specification that Applicants were in possession of these claimed methods at the time of filing.

Applicants' invention is directed to methods of generating multispecific antibodies comprising binding domains for more than one antigen. Applicants have explicitly disclosed that paired light chains having at least 98% sequence identity can very likely be found for any V_L comparison (page 97, lines 6-9). Applicants have disclosed the panning of a large human scFv antibody library for antibodies specific for eleven different antigens that represent considerable variation in structure and function (page 95, line 27 through page 96 line 9). After comparing the V_L sequences of the antibodies, Applicants discovered at least one, and often more than one, light chains having at least 98 % sequence identity for most pair wise comparisons (page 96, line 21 through page 97, line 26, Table 6, Appendix, Figure 4 and Figure 8). Based upon these results, it is likely that light chains that have at least 98% sequence identity can be found for any V_L comparison. In fact, the majority of pairwise comparisons identified light chains having at least 98% sequence identity. These light chains were selected for binding to the specific antigen and, thus, could bind to the specific antigen of choice.

The Examiner contends, however, that the present specification does not contemplate multispecific antibodies comprising light chains having even 1 amino acid difference between them, because the specification allegedly only discloses comparing light chains to identify a single common light chain for use in a multispecific antibody.

The Applicants respectfully disagree, and submit that the specification explicitly suggests the use of common light chains having less than 100% identity, for example, having at least 98% identity. The Examiner's attention is directed to page 97, line 24 to page 98, line 3. Here, the Applicants disclose two light chains that have 98% sequence identity and differ by two residues outside of the antigen binding CDRs. The specification states that these two amino acid changes may have little or no effect on antigen binding (page 97, lines 26-27). The specification concludes that, while the sequence similarity of these light chains makes them candidates for the common light chain of the invention, in an alternative embodiment "according to the invention, such light chains having 98-99% sequence identity with the light chain of a prospective paired scFv (Axl. 78, for example), *may be substituted with the paired light chain and retain binding specificity*" (page 97, line 28 through page 98, line 3) (emphasis added). Therefore, the present specification clearly teaches that light chains having at least 98% sequence identity can be interchangeable in the design of multispecific antibodies of the invention, without having an effect on antigen binding. Applicants respectfully submit, therefore, that one of skill in the art

would readily apprehend that Applicants were in possession of the concept of multispecific antibodies comprising light chains having at least 98% identity.

Applicants respectfully submit that claims 30-42 are amply described in the specification for at least the foregoing reasons. Furthermore, since the claims as amended are fully described by the specification, Applicants submit that no new matter was added by the amendments. Withdrawal of the rejection is respectfully requested.

Claims 50 and 53-55 were rejected under 35 U.S.C. 112, first paragraph, for alleged new matter. The Examiner contends that the specification only supports claims including a limitation that the differences between the sequences of the compared light chains occurs outside the CDRs. Applicants traverse this rejection. The specification explicitly teaches that a light chain having at least 98% identity to a second light chain can be substituted with that light chain while having little or no effect on antigen binding. Therefore, one of skill in the art would readily apprehend that Applicants were in possession of the concept of multispecific antibodies comprising light chains having at least 98% identity.

Applicants respectfully submit that claims 30-42, 50 and 53-55 are amply described in the specification for at least the foregoing reasons. Furthermore, since the claims as amended are fully described by the specification, Applicants submit that no new matter was added by the amendments. Withdrawal of the rejection is therefore requested.

Enablement

Claims 41-42 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. The Examiner contends that the claims are enabled for isolated host cells, but not for host cells comprised within a transgenic animal, or an animal or human being having been treated by gene therapy. Claims 41-42 presently recite that the host cells are isolated host cells. Withdrawal of the rejection is therefore requested.

35 U.S.C. 112, second paragraph

Claims 41-55 were rejected under 35 U.S.C. 112, second paragraph as indefinite. Applicants traverse these rejections.

Regarding claim 41, the Examiner suggested replacing the phrase "a nucleic acid" with "the nucleic acids." Claim 41 has been amended in accordance with the Examiner's suggestion.

Regarding claim 43, the Examiner states that antecedent basis is missing for a claim limitation. This claim has been amended to provide proper antecedent basis.

The Examiner also stated that claim 43 is indefinite because it recites an altered amino acid residue in a first polypeptide that is an amino acid from the at least second polypeptide. Claim 43 has been amended to clarify the nature and location of the altered amino acid residue.

Regarding claim 44, the Examiner contends that this claim merely recites limitations already present in claim 43. Claim 44 has been cancelled.

With respect to claim 45, the Examiner contends that this claim is outside the scope of claim 43. Applicants submit that claim 45 is clearly within the scope of claim 43 as amended.

Regarding claim 50, the Examiner pointed out a subject/verb grammatical error. Claim 50 has been amended to correct this error.

The Examiner also asserted that the phrase "variable light chain" in claim 50 is indefinite. This claim has been amended in accordance with the Examiner's suggestion to recite "variable domain of a light chain."

The Examiner also stated that claim 50 lacks proper antecedent basis for the phrase "the variable light chain." Claim 50 has been amended to provide proper antecedent basis.

Applicants submit that claims 41-55 are definite under 35 U.S.C. 112, second paragraph, and withdrawal of the rejection is therefore requested.

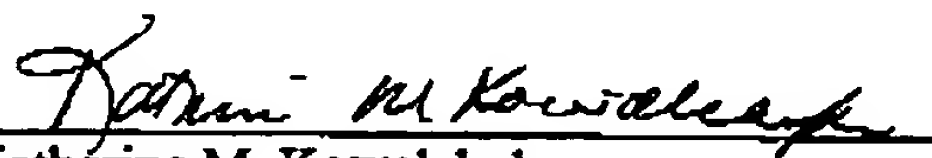
Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332.5300

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Katherine M. Kowalchuk
Reg. No. 36,848

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PATENT TRADEMARK OFFICE